REMARKS

This is a response to a Non-Final Office Action mailed March 25, 2008. With this amendment, no claims have been amended, no claims have been cancelled, and claims 31-37 have been added. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier. Thus, claims 1, 2, 4-6, 12, 13, 24-26 and 28-37 are pending in the application. Support for new claim 31 can be found in paragraph [0105] of the specification. Support for new claim 32 can be found in paragraph [0093] of the specification. Support for new claim 33 can be found in paragraph [0081] of the specification. Support for new claims 34-37 can be found in paragraphs [0037]-[0040] of the specification.

Claim Rejections-35 U.S.C. § 103

Claims 1-2, 4-6, 12-13, 24-26 and 28-30 were rejected to under 35 U.S.C. 103(a) as being unpatentable over the combination of Kley U.S. Patent No. 6,396,054, Kondo et al. (US Pub. No. 2004/0076996), and further in view of Fisher et al. (US Pub No. 2003/0138968). Applicants respectfully traverse this rejection.

Independent claim 1 includes the features, inter alia, "aligning a biomolecule in a parallel manner on a surface by molecular combing" and "wherein the molecular combing comprises attachment of the biomolecule to the surface and alignment of the attached biomolecule by drawing the biomolecule through a moving meniscus." Independent claim 24 includes the features, inter alia, "a surface comprising molecular structures aligned in a parallel manner by molecular combing prior to analysis" and "wherein the molecular structures are biomolecules and the molecular combing comprises attachment of the biomolecules to the surface and alignment of the attached biomolecules by drawing the biomolecule through a moving meniscus." As taught in the specification, molecular combing is a process of straightening and aligning biomolecules. "Thus, removal of the surface from the aqueous medium results in stretching of the bound target molecules, parallel to the direction of movement of the meniscus (paragraph [0042])." "Once the surface has been entirely removed from the aqueous medium, the attached molecules are aligned in a parallel

fashion that may be more easily and accurately analyzed (paragraph [0043])." Although believed unnecessary, Applicants amended independent claims 1 and 24 in the last response to explicitly define molecular combing in these claims as "attachment of the biomolecule to the surface and alignment of the attached biomolecule by drawing the biomolecule through a moving meniscus." (Response at p.2, claim 1, last clause and p.5, claim 24, last clause). This feature is not shown in any of the applied references or any combination of the applied references.

Kley

In the office action, the examiner states that Kley teaches "a) alignment an object on a surface by molecular combing (column 16, lines 50-60 where object is positioning on the x,y plane (aligning object) on a surface (diamond coated surface) (column 16, lines 15-20) by molecular combing (column 17))." (Office action, p.3, l.1-3). Kley, however, does not teach molecular combing. Kley teaches a "scanning probe microscope assembly and corresponding method for making confocal, spectrophotometric, near-field, and scanning probe measurements and forming associated images from the measurements (Abstract)." Indeed, the portions of Kley cited by the Examiner clearly show that Kley does not teach molecular combing. In column 16, lines 15-20, Kley teaches a method of growing a probe tip for the scanning probe microscope:

> The core material 300 or an overlying tungsten, silicon carbide or silicon nitride layer at the sharp end 188 is pushed into or rubbed on a surface containing fine grain diamond (such as a lap or polycrystalline diamond coated surface). The sharp end 188 picks up a seed crystals of diamond. The probe 102 is then placed in a CVD environment for growth of the polycrystalline diamond layer 301 at the seed sites around the sharp end 188. (col.16, l.15-20.)

In column 16, lines 50-60, Kley teaches using a scanning control routine to align the probe with the sample. The sample itself is not stretched and aligned "parallel to the direction of movement of the meniscus," as taught in paragraph [0042] of the instant specification.

> In the case where the upper and lower bounds 502 and 504 are determined by the scanning control routine 122, the scanning control routine 122 controls the making of sample confocol microscopy measurements of the object 104 at

> low and high levels in the z direction. To do so, the scanning control routine 122 generates control signals to control the translator 110 for positioning the object in the x,y plane and generates control signals to control the optics of the microscope 160 for adjusting the confocol region (focol plane) in the z direction. However, those skilled in the art will appreciate that a translator that positions an object in each of the x,y, and z directions could also be used. The scanning control routine 122 then determines from the sample measurements the upper and lower bounds 502 and 504 (z2 and a1) of the object 104 and also the average diameter (n) of the smallest feature detected with the sample measurements. (Col.16, l.50-60).

Column 17 further reinforces that Kley teaches movement and alignment of the probe to the sample:

> Referring to FIG. 11, the scanning control routine 122 then determines at a number of confocol regions 502, 503,and 504 (in the z direction) the bounds of the object 104 in the x,y plane. This is also accomplished with sample measurements made under the control of the scanning control routine in the manner just described. (Col.17, l.8-13).
>
> In the case where the microscope 160 is a spot scanning confocol microscope, then the scanning control routine 122 uses the table to generate control signals to control the translator 110 and the optics of the microscope 16 for making confocol microscopy measurements at each confocol region in the table but only within the bounded area in the x,y plane with the table specifies for it. (Col.17, l.25-31).

Simply, Kley teaches movement of a scanning probe to align it to a sample, not molecular combing, i.e., as "attachment of the biomolecule to the surface and alignment of the attached biomolecule by drawing the biomolecule through a moving meniscus," as recited in independent claims 1 and 24.

Kondo

In the office action, the examiner states that Kondo teaches "aligning a biomolecule in a parallel manner on a surface (abstract second paragraph; page 3, column 1, [0026]; and page 4, column 1, [0042]) and wherein the molecular combing comprises attachment of the biomolecule to a surface (connections with peripheral surface) (page 5, column 1, [0058-0059]) and alignment of

the attached biomolecule (abstract, second paragraph; page 3, column 1, [0026]; and page 4, column 1, [0042])." (Office action, p.3, l.18-22). Kondo, however, does not teach molecular combing. Kondo teaches a gene analysis method and analyzer (Title)." The portions of Kondo cited by the Examiner clearly show that Kondo does not teach molecular combing.

> It relates to a gene analysis method comprising the steps of extracting a target nucleic acid from a biological sample (23) and amplifying a target DNA, thereafter, introducing a reaction eluent (L) containing a predetermined DNA into a stationary-phase DNA probe (53) having a predetermined temperature and arranged in series or in parallel and separating a DNA complementary to the stationary-phase DNA probe (53). (Abstract)
>
> The present invention provides a gene analysis method comprising the steps of extracting a target nucleic acid from a biological sample and amplifying a target DNA, thereafter, introducing a reaction eluent containing a predetermined DNA into a stationary-phase DNA probe having a predetermined temperature and arranged in series or in parallel and separating a DNA complementary to the stationary-phase DNA probe, characterized in that the gene analysis method comprises a plurality of stationary-phase DNA probes at least a part of which can be set to a temperature for forming a double strand of a DNA to be tested and a reaction eluent containing the same or different kinds of DNA after being amplified is introduced into the stationary-phase DNA probes. Accordingly, detection of various kinds of DNA can be conducted rapidly and with precision, analysis of a plurality of genes can be made simultaneously from different kinds of samples, and a double strand forming position of the DNA to be tested can be detected rapidly. (Paragraph [0026]).
>
> According to the present invention, a plurality of the same or different stationary-phase DNA probes are received in a plurality of columns which are arranged in parallel with each other and fluid resistance means having a larger fluid resistance than that of the column portions is disposed at each supply passageway of an eluent which is in communication with each of the columns. By reducing the flow rate of each feed passage of the eluent, the flow rate of the column part can be restrained from being varied. Thus, the parallel connection of the plural columns, the parallel treatment of the DNA detection thereof and supply of the eluent by only one feed eluent pump can be realized. In addition, the device of this type can be made compact in size and light in weight. (Paragraph [0042]).

> FIG. 10 is a sectional view showing, on an enlarged basis, an essential portion of a DNA detector which is applied to a fifth embodiment of the present invention and in which a plurality of narrow tubes are arranged in an axial direction of the tubes on an outer peripheral surface of a tubular heat block and a stationary-phase DNA probe is filled in each tube. (Paragraph [0058]).
>
> FIG. 11 is an explanatory view showing an application example of FIG. 10, in which the narrow tube is spirally wound around the outer peripheral surface of the tubular heat block. (Paragraph [0059]).

That is, Kondo teaches a device which has stationary capture probes which are arranged in series or parallel. After amplification, the target nucleic acid is contacted with the array of capture probes. Further, the device may have a plurality of columns arranged in parallel and having capture probes within. Nowhere does Knodo teach or suggest molecular combing, i.e., "attachment of the biomolecule to the surface and alignment of the attached biomolecule by drawing the biomolecule through a moving meniscus," as recited in independent claims 1 and 24.

Fisher

In the office action, the examiner states that Fisher teaches "a method wherein a molecular combing (arrangement of biomolecules to standard of biochemistry/molecular biology) (page 6, [0057-00581) comprises attachment of the biomolecule to the surface (page 5, column 2, first 10 lines) and alignment of the attached biomolecule by drawing the biomolecule through a moving meniscus (page 3, column 2, [0035] and page 4, column 2, [0042])." (Office action, p4, l. 5-9). Fisher, however, does not teach molecular combing. Fisher teaches a liquid transfer device in which "[l]iquids are transferred from a plurality of wells or depots having openings arranged in a selected format to one or more receptacles, by displacing liquid contained in each well so that a convex meniscus swells from the opening, and contacting the receptacle with the swollen meniscus to draw a portion of the liquid into the receptacle (Abstract)." The portions of Fisher cited by the Examiner clearly show that Fisher does not teach molecular combing.

> As the drawings show by way of illustration, the invention is embodied in apparatus for direct non-contact transfer of fluids from a plurality of depots, or wells, having openings arranged in a specified pattern, to a plurality of receptacles arranged in a corresponding or complementary pattern. In

particular embodiments the liquid contained in the wells is displaced so that a convex meniscus swells outward from the openings, and the liquid flows into the receptacles upon contact of the receptacle with the convex meniscus. The flow of the liquid into the receptacle following contact of the receptacle with the meniscus is at least initially a result of capillary interaction. (Paragraph [0035]).

The prototype constructed in this fashion and having these dimensions and operated generally as described above with reference to FIG. 1C, using water as a liquid for purposes of demonstration, proved capable of raising a convex meniscus to a height of about 1 mm away from the opening at the surface of the depot block. For purposes of demonstration the orifice plate of a print head was brought into generally parallel proximity to the surface of the depot block, with the print head orifices approximately aligned with the centers of the depots. As the orifice plate was moved close enough to the depot block, the print head orifice contacted the convex meniscus, and substantially all the liquid that had been displaced through the opening was transferred into the print head through the print head orifice. (Paragraph [0042]).

The embodiment of FIGS. 2A and 2B can be employed in the method of the invention as follows. Referring to FIG. 2B, which generally as in FIG. 1C is a composite showing a time course (t.sub.0 through t.sub.4) from left to right, a quantity of liquid 100 is held in each depot. As described above with reference to FIG. 1C, the depots may be entirely filled with the liquids or, as illustrated in FIG. 2B (t.sub.0), they may be only partly full. Transfer from a depot is initiated (t.sub.1) by applying a force against the deformable wall portion 29, deforming it inward and displacing the liquid 100 within the depot. The wall may be deformed by any of a variety of means for applying force; one such means, shown by way of illustration in FIG. 2B, is to press a plunger 108 inwardly against the outer surface of the deformable wall portion. *This results in a progressive collapse (t_1 through t_3) of the deformable wall portion 29, which causes the meniscus 102 of the liquid to rise toward (t.sub.1) and through (t_2) the opening 25, forming a convex meniscus 104. As the liquid 100 is further displaced (t_3) the convex meniscus 104 rises and swells as a droplet 106 of the liquid is held by surface interaction away from the opening 25 and the depot block surface 21. The transfer is completed (t_4) by contacting the swollen convex meniscus 104 with a receptacle 110, which may for example be an orifice 112 in a planar receiving member 114. Surface interaction of the receptacle 110 with the liquid results in movement of the droplet of fluid 106 away from the depot block surface 21 and the opening 25 and into the receptacle 110.* (Paragraph [0048])(emphasis added to portion cited by examiner - page 5, column 2, first 10 lines).

> Other embodiments are within the following claims. For example, the depots may be arranged in other formats, standard to biochemistry and molecular biology or not. For transfer of a multiplicity of liquids in a single transfer step, all that is required of the format is that the depot openings and the receptacle openings be arranged in a format that permits bringing a multiplicity of receptacles into contact with the multiplicity of swollen menisci nearly all at once. That is, the respective receptacles and depot openings need only be arranged such that they can be brought into generally parallel proximity in a single transfer step. (Paragraph [0057]).
>
> For example, either the depot openings or the receptacles can be arranged on or in a generally planar support, and the other can be arranged generally on or in a cylindrical support; and the cylindrical support can be rotated about an axis parallel to the planar support and translated over it as if it were rolling upon an imaginary plane sufficiently close to the planar support that the receptacles contact swollen menisci at the depot openings and draw up the droplets as the movement progresses. Or, the depot openings and the receptacles each can be arranged on or in a generally cylindrical support, and the cylinders can be rolled to bring succeeding receptacles into contact with succeeding menisci. Other configurations will be apparent, and are within the scope of the invention. (Paragraph [0058])

Simply, Kondo teaches a device in which fluid is pushed out of reservoirs (depots) in a lower block and sucked up into a small opening in a receptacle through capillary action. Kondo is merely a fluid transfer device. Nowhere does Knodo teach or suggest molecular combing, i.e., "attachment of the biomolecule to the surface and alignment of the attached biomolecule by drawing the biomolecule through a moving meniscus," as recited in independent claims 1 and 24. Indeed, Kondo does not even teach biomolecules in the fluid.

Additionally, the Examiner argues "[m]odifying Kley according to Fisher would be able to comprise attachment of the biomolecule to a surface and alignment of the attached biomelecule by drawing the biomolecule through a moving meniscus. This would improve processing because it would help transfer small quantities of liquids from multiplicity of depots to a multiplicity of receptacles (page 1, column 1, [000 11) and therefore, it would have been obvious to one of the ordinary skill in the art to modify Kley according to Fisher." However, "[i]f the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivations to make the proposed modification. *In re*

Gordon, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). Molecular combing as defined in the specification and recited in independent claims 1 and 24 entails **"attachment of the biomolecule to the surface and alignment** of the attached biomolecule by drawing the biomolecule through a moving meniscus." The device and process of Fisher, however, requires a complete transfer of fluid from the depots to the receptacles. Simply, the device of Fisher could not work in combination with Kley and Kondo, or indeed any reference, to perform the claimed molecular combing - **"attachment of the biomolecule to the surface and alignment** of the attached biomolecule by drawing the biomolecule through a moving meniscus." (Independent claims 1 and 24).

Because the Examiner has failed to make a prima facie case for obviousness, Applicants respectfully request withdrawal of the rejection.

CONCLUSION

It is respectfully submitted that each of the presently pending claims are in condition for allowance and notification to that effect is requested. Examiner is invited to contact the Applicants' representative at the below-listed telephone number if it is believed that the prosecution of this application may be assisted thereby.

Dated: June 25, 2008

Respectfully submitted,

By /Martin Sulsky/
Martin Sulsky
Registration No.: 45,403
DARBY & DARBY P.C.
P.O. Box 770
Church Street Station
New York, New York 10008-0770
(202) 639-7514
(212) 527-7701 Fax
Attorneys/Agents For Intel Corporation